REMARKS

Claim 7 has been cancelled. Claims 1-6 and 8-12 have been amended. Claims 1-6 and 8-12 are now pending in this application. Support for the amendments is found in the existing claims and the specification as discussed below. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

The present invention

Prior to the present invention, adsorbed and adjuvanted immunogenic combination compositions gave predominantly a Th-2 stimulating immune response. As explained in the present specification at page 2, lines 28-34:

> Conventional vaccines allow the combination of different antigens, but only within the group of either adjuvanted vaccine components or within the group of non- adjuvanted live-attenuated vaccine relevant organisms. The former group which is adjuvanted by mineral salts primarily gives lead to a Th2 response which is protective for the mentioned diseases, whereas similar adjuvantation could have an inhibitory effect on the immune response necessary for protection against the live attenuated vaccine components (E. B. Lindblad et al., Infect. Immun. 65 (2): 623-629 (1997)).

The group of adjuvanted vaccine components (Group I) gives lead to a Th-2 response such as raising protective antibodies. However, the adjuvants of Group I, inhibit the effects of non-adjuvanted live-attenuated vaccine relevant organisms (Group II). Nevertheless, the diseases covered by the live-attenuated immunogenic compositions of Group II often require a Th-1 type immune response as protecting against these diseases which does not depend upon antibody response alone. Immunogenic combination compositions providing both a sufficient Th-1 and sufficient Th-2 response ***within the same vaccine preparation*** have not been known in the art before Applicants' invention. Additionally, the importance of a negatively charged adjuvant was not recognized in the prior art at the time of the claimed invention.

The present invention demonstrates for the first time and unexpectedly that immunogenic combinations may be prepared in which the Th-1 and Th-2 response against a given antigenic epitope is ***predetermined***. Immunogenic antigens against which a Th-2 response is required are mixed with the negatively charged mineral adjuvant of the invention. The antigens against which

a Th-1 response is required, are subsequently added as the corresponding oligonucleotide sequence encoding for it.

The inventors have demonstrated the general applicability of the invention by preparing immunogenic compositions in which one deliberately predetermines the immunogenic compositions to induce a Th-1 response against one component (Hepatitis B core antigen) while at the same time deliberately inducing a Th-2 response against another component (Hepatitis B surface antigen) and vise versa. Such predetermination is novel and generally applicable as a tool in vaccine design.

The present invention shows, to the best of inventors' knowledge, for the first time the potential of designing immunogenic combination compositions for diseases against which a pronounced Th-1 type immunity is required for protection against one disease, whereas at the same time a Th-2 type immunity is required for protection against another disease. This is important as there are diseases where promoting the wrong kind of immune response does not induce protection. Previous adsorbed immunogenic combination compositions adjuvanted in the traditional way by mineral adjuvants do not have this potential. Hence, the present invention opens up new approaches in the preparation of efficient combination vaccines.

In addition, the present inventors have demonstrated for the first time that surprisingly, by using the immunogenic combination formulations of the present invention, the immune responses against the antigens as such were dramatically enhanced (see Figure 1 of the application). Hence, in application of the claimed technology, there is a synergistic effect and the possibility of reducing the antigen dose, while maintaining a high antibody response.

Rejection under 35 U.S.C. § 112, first paragraph -scope of enablement

Claims 1-11 are rejected under 35 U.S.C. § 112, first paragraph because the specification, while being enabling for an immunogenic composition suitable for administration to a vertebrate host, which comprises: (a) a polynucleotide vaccine component comprising a polynucleotide encoding a vaccine Hepatitis B surface antigen, such that introduction of polynucleotide into said vertebrate host results in expression of a biologically effective amount of same antigen so as to induce a prophylactic or therapeutic immune response; (b) a protein antigen vaccine component comprising a protein antigen selected from the group consisting of bovine serum albumin, hen egg lysozyme and Hepatitis B surface antigen; and (c) a mineral -based, negatively charged

adjuvant, does not reasonably provide enablement for a vaccine composition suitable fore administration to a vertebrate host, which comprises: (a) a polynucleotide vaccine component comprising at least one polynucleotide encoding at least one antigen, such that introduction of said formulation into said vertebrate host results in expression of a biologically effective amount of said antigen or antigens so as to induce a prophylactic or therapeutic immune response; (b) a protein antigen vaccine component comprising at least one protein antigen selected form the group consisting of model protein antigens and vaccine protein antigens; and (c) a mineral-based , negatively charged adjuvant.

This ground of rejection is addressed in part by amendment of the claims and in part by argument.

The claims have been amended to replace "vaccine" with "immunogenic". Support is found throughout the specification which is directed to producing or enhancing an immune response. See the specification, for example at page 6, line 12, lines 19-20, and 27. Immunogenic compositions and methods of preparing immunogenic compositions are clearly supported by the specification which teaches immunogenic compositions comprising a polynucleotide immunogenic component and a protein antigen immunogenic component along with a mineral-based, negatively charged adjuvant. One skilled in the art would be able to identify polynucleotide immunogenic components and protein antigen immunogenic components appropriate to combine and thus obtain compositions falling within the scope of the claims. Furthermore, the specification teaches how to prepare the claimed compositions by mixing the immunogenic components with the mineral-based, negatively charged adjuvant (see experimental section beginning on page 9 of the present specification).

Although the experimental section is directed to combinations of a polynucleotide immunogenic component encoding a vaccine Hepatitis B surface antigen, a protein antigen immunogenic component which is bovine serum albumin, hen egg lysozyme or Hepatitis B surface antigen, and a mineral -based, negatively charged adjuvant, the described method may be generally applied to other combinations of polynucleotide immunogenic components and protein antigen immunogenic components as discussed above. The inventors have demonstrated the general applicability of the invention by preparing immunogenic compositions in which the ability of the immunogenic compositions to induce a Th-1 response against one component

(Hepatitis B core antigen) is deliberately predetermined while at the same time deliberately inducing a Th-2 response against another component (Hepatitis B surface antigen) and vise versa indicating that the methods and compositions are generally applicable as a tool in vaccine design.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 5 and 9 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 has been amended to employ Markush language.

The preamble of claim 9 has been amended to correspond to the method steps.

In addition, claim 10 has been amended for further clarification and to correct clerical error.

In view of Applicants' amendments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 102(b)

Claims 1-6 and 8-12 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Dalemans, et al. (WO 99/30733).

The Office Action states that Dalemans, et al. teach combination vaccines comprising nucleic acid and a polypeptide in combination with adjuvants, that Dalemans, et al. teach the prior mixing of the polypeptide or protein antigen with the adjuvant and a method of use in a combined DNA/ protein vaccine composition. Regarding Applicants' previous arguments, the Office Action states discovery of a new property of a prior art composition does not confer patentability, that the order for mixing components is not recited in the claims, that there is no structural difference between Dalemans, et al. and the present invention, and, regarding claims 1 and 9, that the recitation after the "wherein" clause is given no patentable weight.

First, claim 9 either as previously presented or as currently amended does not include a "wherein" clause. Rather claim 9 (as now amended) recites "preincubating or subsequently

mixing the mineral-based, negatively charged adjuvant with said at least one protein antigen immunogenic component prior to being formulated with said polynucleotide immunogenic component". Accordingly, claim 9 specifies the order of the mixing which must be considered for a determination of patentability.

Furthermore, claim 1 has been amended to include process steps. Specifically, claim 1 has been amended to recite "said composition produced by a method comprising preincubating or subsequently mixing said mineral-based negatively charged adjuvant with said at least one protein antigen immunogenic component prior to formulating with said polynucleotide immunogenic component". Accordingly, the order of mixing the mineral-based negatively charged adjuvant with the protein antigen immunogenic component and formulation with the polynucleotide immunogenic component is now set forth in claim 1.

As set forth in M.P.E.P. section 2113,

> The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product.

In the present case, the process steps describe a structural difference with respect to the cited prior art reference which can only be defined by the process steps as recited in amended claim 1. In this regard, Applicants point out that the order of mixing clearly changes the outcome. For instance, if [A] can bind to either [B] or [C], a prior mixing of [A] + [B], with a subsequent addition of [C] gives [A,B] + [C], a prior mixing of [A] + [C], with a subsequent addition of [B] gives [A,C] + [B]. Clearly, the order of mixing provides a different end-result although the initially used components are identical.

Applicants emphasize that the order of mixing the components of the composition results in a structure in toto which differs from the structures of the compositions which were made by a different order of mixing the components. The different structure is exemplified by a different effect, inter alia a significantly enhanced immunogenicity of the polynucleotide component, compared to another order of admixing the components or the omission of the adjuvant. This is extensively described in the application and corroborated by the examples. The eventual product is characterized by the process by which it is made.

The immunogenic composition of the invention was not known

As discussed above, the claims have been amended to clearly specify the order of mixing of components. The specific order of mixing, which was neither disclosed nor suggested in Dalemans, et al., is important for achieving a specific end-result. This specific end-result was neither disclosed nor suggested in the prior art, i.e. the immunogenic composition of the present invention provides effects different from known vaccine compositions. Accordingly, the immunogenic compositions of the presently claimed invention are not anticipated by Dalemans, et al..

Dalemans does not teach the order of mixing as presently claimed

Dalemans, et al. do not teach or suggest "said composition produced by a method comprising preincubating or subsequently mixing said mineral-based negatively charged adjuvant with said at least one protein antigen immunogenic component prior to formulating with said polynucleotide immunogenic component" as now claimed (claim 1 as amended). In fact, Dalemans, et al. teach administrating of the DNA and protein in the "vaccine" at the same time (see Dalemans, et al., page 3, line 30; page 4, lines 6-8; page 7, line 15; and claim 22). One of ordinary skill in the art, based upon the disclosure of Dalemans, et al., would administer the DNA and protein simultaneously, as taught by Dalemans, et al. and there is no teaching on admixing the compounds in any specific order. Dalemans does not provide any order of mixing the components, let alone preincubating or mixing said mineral-based negatively charged adjuvant with a protein antigen vaccine component prior to formulating with a polynucleotide vaccine component as required by the present invention. Accordingly, this feature of the invention is neither taught nor suggested by Dalemans, et al.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Dalemans does not teach the use of adjuvants as presently claimed

Dalemans, et al. teach away from the claimed invention in teaching that the use of immunostimulants (adjuvants) may be obviated. See page 5, first paragraph of Dalemans, et al. which is reproduced below:

> Another benefit of the present invention is that in certain cases, where there is a predisposition to a strong immune response (e. g., high percentage of responders to initial vaccination, high level of antibody titers, CTL response, etc.), the

combination of both compounds (DNA + protein) can obviate the need for immunostimulants.

Furthermore, the suggestion of Dalemans, et al. in the section reproduced above to use vehicles which do not bias the immune response would also be viewed by one of ordinary skill in the art to teach away from the claimed invention as mineral adjuvants bias the immune response towards Th-2.

Dalemans, et al. is silent regarding the effects of the different adjuvants and the importance of electric charge. Dalemans merely provides a very general list on adjuvants without specifying a preference for mineral-based negatively charged adjuvants, and including adjuvants which do not work. Dalemans, et al. teach that it is preferable not to use an adjuvant at all.

Accordingly, based upon Dalemans, et al., one of ordinary skill in the art would not use an adjuvant at all, contrary to the claimed invention.

Dalemans, et al. do not provide an enabling disclosure

Referring to the points raised in the scope of enablement rejection of the Examiner's Final Office Action, Applicants point out that these same points are pertinent to the disclosure of Dalemans, et al.

For example,

- Dalemans does not demonstrate any in vivo protective immunity (cf. Boslego et al.).
- Dalemans does not provide challenge experiments.
- Dalemans provides no teaching of the most effective route of administration (cf. Ellis).
- Dalemans contemplates that correct folding of the protein is achieved when said protein is encoded by a gene via intracellular expression (Dalemans, et al. page 7, lines 1-7).
- Dalemans connotes delayed response of the protein component (thus without an adjuvant).
- Dalemans requires that the epitope encoded by the polynucleotide is identical to the epitope of the polypeptide. On page 4, lines 19-21 it is stated that "This enhancement is specific to the polynucleotide added, as a similar polynucleotide not encoding the specific polypeptide was unable to enhance the immune responses." Example 6 demonstrates the same. All experiments are performed with the same epitope on both the polypeptide and the polynucleotide (Note that R5V-G has not been tested).

- The synergistic effect of Dalemans is not conclusive, since different amounts of polypeptide and/or polynucleotide are used in the different experiments, including the control experiments.
- In the Dalemans experiments, only antibody titers are increased, relative to the "control" experiments (see Figure 1).
- Dalemans provides no conclusive results regarding the cellular response of the various combinations, i.e. proliferation vs. IL-S vs. IFNy vs. CfL responses (see Table 1).

Accordingly, Dalemans, et al. do not provide an enabling disclosure.

Summary

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Claim objections

The spelling of "polynucleotide" in claim 1 has been corrected by amendment.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims in any jurisdiction are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application. Any amendments made by way of the present paper, and the observations contained herein, are made solely for the purposes of the prosecution of this U.S. Patent application and without prejudice to the Applicant in other jurisdictions.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: July 22, 2008

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